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L5 ANSWER 1 OF 8 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2002219361 EMBASE
TI The **SOCS box:** A tale of destruction and degradation.
AU Kile B.T.; Schulman B.A.; Alexander W.S.; Nicola N.A.; Martin H.M.E.; Hilton D.J.
CS B.T. Kile, Walter and Eliza Hall, Institute of Medical Research, Coop. Res. Ctr. Cell. Growth Factors, Parkville, Vic. 3050, Australia. hilton@wehi.edu.au
SO Trends in Biochemical Sciences, (1 May 2002) 27/5 (235-241).
Refs: 60
ISSN: 0968-0004 CODEN: TBSCDB
PUI S 0968-0004(02)02085-6
CY United Kingdom
DT Journal; General Review
FS 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LA English
SL English
AB Although initially identified in the suppressor of cytokine signaling (**SOCS**) family of proteins, the C-terminal **SOCS box** has now been identified in more than 40 proteins in nine different families. Growing evidence suggests that the **SOCS box**, similar to the F-box, acts as a bridge between specific substrate-binding domains and the more generic proteins that comprise a large family of E3 ubiquitin protein ligases. In this way, **SOCS** proteins regulate protein turnover by targeting proteins for polyubiquitination and, therefore, for proteasome-mediated degradation.

L5 ANSWER 2 OF 8 MEDLINE
AN 2002105227 MEDLINE
DN 21825157 PubMed ID: 11837794
TI Suppressors of cytokine signaling (**SOCS**): inhibitors of the JAK/STAT pathway.
AU Cooney Robert N
CS Department of Surgery, The Pennsylvania State University College of Medicine, Hershey 17033, USA.
NC GM-55639 (NIGMS)
SO SHOCK, (2002 Feb) 17 (2) 83-90. Ref: 93
Journal code: 9421564. ISSN: 1073-2322.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200208
ED Entered STN: 20020212
Last Updated on STN: 20020820
Entered Medline: 20020819
AB The suppressors of cytokine signaling (**SOCS**) are recently identified inhibitors of cytokine and growth factor (GF) signaling that act via the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway. Cytokine-mediated JAK/STAT signaling controls a number of important biologic responses, including immune **function**, cellular growth, differentiation, and hematopoieses. The **SOCS** family consists of eight proteins: CIS and SOCS1-SOCS7, which contain a central SH2 domain, a conserved C-terminus referred to as the **SOCS box**, and a unique N-terminus. The expression of **SOCS**-1 to -3 and CIS is induced by cytokine or GF stimulation, resulting in the inhibition of JAK/STAT-mediated cytokine signaling by

what appears to be a classic negative feedback loop. In this article we **review** cytokine/GF signaling by the JAK/STAT pathway, discovery of the **SOCS** family, the regulation of **SOCS** expression, mechanism(s) of **SOCS** action, and we summarize some of the biochemical and genetic studies investigating the physiologic role of **SOCS** in regulating cytokine **activity.**

L5 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
AN 2001:888643 CAPLUS
DN 136:133173
TI The suppressors of cytokine signalling (**SOCS**)
AU Kile, B. T.; Alexander, W. S.
CS Division of Cancer and Hematology, The Walter and Eliza Hall Institute for Medical Research and the Cooperative Research Centre for Cellular Growth Factors, Post Office, Royal Melbourne Hospital, Victoria, 3050, Australia
SO Cellular and Molecular Life Sciences (2001), 58(11), 1627-1635
CODEN: CMLSFI; ISSN: 1420-682X
PB Birkhaeuser Verlag
DT Journal; General Review
LA English
AB A **review** discussed the suppressors of cytokine signaling. Members of the **SOCS** (suppressor of cytokine signaling) family of proteins play key roles in the neg. regulation of cytokine signal transduction. A series of elegant biochem. and mol. biol. studies has revealed that these proteins act in a neg. feedback loop, inhibiting the cytokine-activated Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway to modulate cellular responses. Although structurally related, the precise mechanisms of **SOCS**-1, **SOCS**-3 and cytokine-inducible SH2-contg. protein (CIS) action vary. Direct interaction of **SOCS** SH2 domains with the JAK kinases or cytokine receptors allows their recruitment to the signaling complex, where they inhibit JAK catalytic **activity** or block access of the STATs to receptor binding sites. The defining feature of the family, the C-terminal **SOCS box** domain, appears dispensable for these actions but is likely to play a key role in neg. regulation of signaling by targeting mols. assocd. with the **SOCS** proteins for degrdn. The relevance of **SOCS**-mediated regulation of cytokine responses has been brought into sharp focus by the dramatic phenotypes of mice lacking these regulators. Indispensable roles for members of this family have been identified in the regulation of interferon .gamma., growth hormone and erythropoietin, and the absence of **SOCS**-1 or **SOCS**-3 is lethal in mice.
RE.CNT 94 THERE ARE 94 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 2000:871131 CAPLUS
DN 135:75305
TI JAK/STAT pathway and its negative regulation
AU Yoshimura, Akihiko; Hanada, Toshikatsu; Kanizono, Shintaro
CS Institute of Life Science, Kurume University, Japan
SO Jikken Igaku (2000), 18(15), 2001-2008
CODEN: JIIGEF; ISSN: 0288-5514
PB Yodosha
DT Journal; General Review
LA Japanese
AB A **review** with 30 refs. discussing role of JAK/STAT in cytokine signaling pathways. Topics included are neg. regulatory mechanism of cytokine signaling, neg. feedback factor CIS (cytokine inducible SH2-protein) induced by STAT5, CIS family and **SOCS-box**, JAK/STAT inhibitory **function** by CIS3, and physiol. **function** of JAB, CIS3, and SOCS2.

L5 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 2000:720210 CAPLUS
DN 134:294122
TI The suppressors of cytokine signaling (**SOCS**) proteins: Important feedback inhibitors of cytokine action
AU Nicola, N. A.; Greenhalgh, C. J.
CS The Walter and Eliza Hall Institute of Medical Research and the Cooperative Research Centre for Cellular Growth Factors, Parkville, Victoria, Australia
SO Experimental Hematology (New York) (2000), 28(10), 1105-1112
CODEN: EXHMA6; ISSN: 0301-472X
PB Elsevier Science Inc.
DT Journal; General Review
LA English
AB A **review** with 57 refs. While pos. effectors of cytokine signaling pathways are relatively well defined, neg. regulation can be just as important but is poorly understood. The recently discovered suppressor of cytokine signaling (**SOCS**) family of proteins has been implicated in the neg. regulation of several cytokine pathways, particularly the receptor-assocd. tyrosine kinase/signal transducer and activator of transcription (JAK/STAT) pathways of transcriptional activation. Biochem. studies revealed that inhibition can occur via a variety of mechanisms. **SOCS** proteins bind to tyrosine-phosphorylated residues of target proteins via their SH2 domains, then inhibit JAK **activity** through their N-terminal domains, and are thought to induce degrdn. of bound mols. through a conserved **SOCS-box** motif that interacts with the proteasome. **SOCS** protein expression is induced by a wide variety of cytokines with each member displaying varying kinetics of induction. Gene modification studies in mice have demonstrated that **SOCS**-1 has a clear role in the neg. regulation of interferon-.gamma. signaling, while other **SOCS** family members have also been shown to be involved in the regulation of T cell, growth hormone, and erythropoietin signaling systems.
RE.CNT 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 2
AN 1999:682145 CAPLUS
DN 132:11447
TI Suppressors of cytokine signaling (**SOCS**): negative regulators of signal transduction
AU Alexander, Warren S.; Starr, Robyn; Metcalf, Donald; Nicholson, Sandra E.; Farley, Alison; Elefanty, Andrew G.; Brysha, Marta; Kile, Benjamin T.; Richardson, Rachel; Baca, Manuel; Zhang, Jian-Guo; Willson, Tracy A.; Viney, Elizabeth M.; Sprigg, Naomi S.; Rakar, Steven; Corbin, Jason; Mifsud, Sandra; DiRago, Ladina; Cary, Dale; Nicola, Nicos A.; Hilton, Douglas J.
CS The Walter and Eliza Hall Institute of Medical Research and the Cooperative Research Centre for Cellular Growth Factors, Post Office, Royal Melbourne Hospital, Victoria, 3050, Australia
SO Journal of Leukocyte Biology (1999), 66(4), 588-592
CODEN: JLBIE7; ISSN: 0741-5400
PB Federation of American Societies for Experimental Biology
DT Journal; General Review
LA English
AB A **review** with 23 refs. **SOCS**-1 was originally identified as an inhibitor of interleukin-6 signal transduction and is a member of a family of proteins (**SOCS**-1-**SOCS**-7 and CIS) that contain an SH2 domain and a conserved C-terminal **SOCS box** motif. Mutation studies have established that crit.

contributions from both the N-terminal and SH2 domains are essential for **SOCS**-1 and **SOCS**-3 to inhibit cytokine signaling. Inhibition of cytokine-dependent activation of STAT3 occurred in cells expressing either **SOCS**-1 or **SOCS**-3, but unlike **SOCS**-1, **SOCS**-3 did not directly interact with or inhibit the **activity** of JAK kinases. Although the conserved **SOCS box** motif appeared to be dispensable for **SOCS**-1 and **SOCS**-3 action when overexpressed, this domain interacts with elongin proteins and may be important in regulating protein turnover. In gene knockout studies, **SOCS**-1-/- mice were born but failed to thrive and died within 3 wk of age with fatty degeneration of the liver and hemopoietic infiltration of several organs. The thymus in **SOCS**-1-/- mice was small, the animals were lymphopenic, and deficiencies in B lymphocytes were evident within hemopoietic organs. The authors propose that the absence of **SOCS**-1 in these mice prevents lymphocytes and liver cells from appropriately controlling signals from cytokines with cytotoxic side effects.

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L5 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 1998:648404 CAPLUS
DN 130:2854
TI **SOCS**: suppressors of cytokine signaling
AU Starr, Robyn; Hilton, Douglas J.
CS The Cooperative Research Centre for Cellular Growth Factors and The Walter and Eliza Hall Institute of Medical Research, Parkville, 3052, Austria
SO International Journal of Biochemistry & Cell Biology (1998), 30(10), 1081-1085
CODEN: IJBBFU; ISSN: 1357-2725
PB Elsevier Science Ltd.
DT Journal; General Review
LA English
AB A **review** with 13 refs. Regulation of many aspects of cell behavior occurs through the interaction of cytokines with specific cell surface receptors, resulting in the activation of cytoplasmic signal transduction pathways. Although cellular responses to cytokines are tightly controlled, few mols. have been identified which are able to switch these signals off. The suppressors of cytokine signaling (**SOCS**) proteins are a new family of neg. regulators of cytokine signal transduction. **SOCS** proteins contain a variable amino-terminal region, a central Src-homol. 2 (SH2) domain and a novel conserved carboxy-terminal motif termed the **SOCS box**. The expression of **SOCS** proteins is induced by cytokine. Once expressed, **SOCS** downregulate JAK/STAT pathways and hence the biol. response. Recent studies, primarily reliant on overexpression of proteins, indicate that **SOCS** may be involved in modulating addnl. pathways, suggesting that they may play a more general role in regulating cellular responses to cytokine. The anal. of knockout mice will clarify the physiol. role of **SOCS** in regulating cytokine responsiveness. Mutations leading to the loss of **SOCS** **activity** may give rise to cytokine hyperresponsiveness and may contribute to the development of diseases such as diabetes and cancer. Small mol. effectors which modify **SOCS function** may potentially be useful therapeutics for the treatment of certain diseases.

RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 1998:360446 CAPLUS
DN 129:107597
TI The **SOCS** proteins: a new family of negative regulators of signal

transduction
AU Nicholson, Sandra E.; Hilton, Douglas J.
CS The Walter and Eliza Hall Institute for Medical Research and The Cooperative Research Center for Cellular Growth Factors, Parkville, 3050, Australia
SO Journal of Leukocyte Biology (1998), 63(6), 665-668
CODEN: JLBIE7; ISSN: 0741-5400
PB Federation of American Societies for Experimental Biology
DT Journal; General Review
LA English
AB A **review** with 15 refs. The neg. regulation of cytokine signaling, with the exception of the tyrosine phosphatases, is not widely understood. The authors recently identified a new family of neg. regulators by retroviral expression of hematopoietic cDNA library in the monocytic leukemic cell line, M1. This was coupled with selection for cells that were no longer able to differentiate in response to interleukin-6. From this screen, **SOCS**-1 was cloned and was shown to arrest cytokine signaling by binding to and inhibiting the intrinsic enzymic **activity** of the JAK family of protein tyrosine kinases. **SOCS**-1 expression is induced in response to a range of cytokines and as such is thought to form part of a classic neg. feedback loop. The **SOCS** family of proteins is linked by the presence of a conserved C-terminal domain termed the **SOCS box** and now encompasses 5 distinct groups on the basis of the structural elements found N-terminal to the **SOCS box**: (1) those that contain SH2 domains, (2) those that contain WD-40 repeats, (3) ankyrin repeats, (4) SPRY domains, and (5) GTPase domains. As yet the **function** of the **SOCS box** remains unknown, but given the level of conservation within such diverse proteins, it is likely to have a broadly similar role in each.
RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
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